

CLAIMS

What is claimed is:

1. A compound represented by the structural formula:

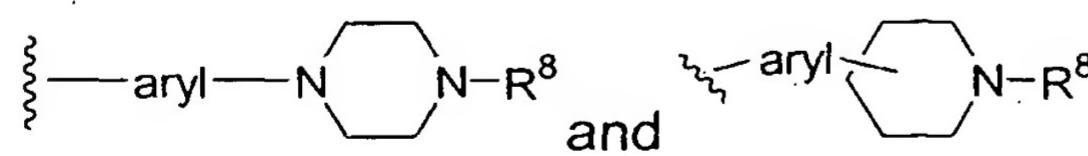
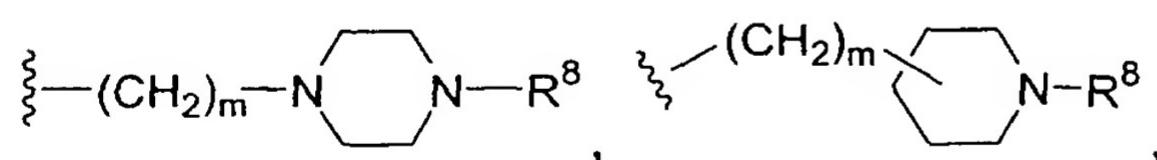


5 Formula III

wherein:

- R is selected from the group consisting of alkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, arylalkyl, cycloalkyl, -NR⁶R⁷, -C(O)R⁷, -C(O)OR⁶, -C(O)NR⁶R⁷ and -S(O₂)R⁷, wherein each of said alkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, CF₃, CN, -OCF₃, -OR⁶, -C(O)R⁷, -NR⁶R⁷, -C(O)OR⁶, -C(O)NR⁶R⁷, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁶R⁷, -N(R⁵)S(O₂)R⁷, -N(R⁶)C(O)R⁸ and -N(R⁵)C(O)NR⁶R⁷ and NO₂;

- R² is selected from the group consisting of hydrogen, R⁹, alkyl, alkenyl, alkynyl, alkenylalkyl, alkynylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, -CF₃, -C(O)R⁷, -NR⁶R⁷, -C(O)OR⁶, -C(O)NR⁵R⁶, alkyl substituted with 1-6 R⁹ groups which groups can be the same or different with each R⁹ being independently selected,

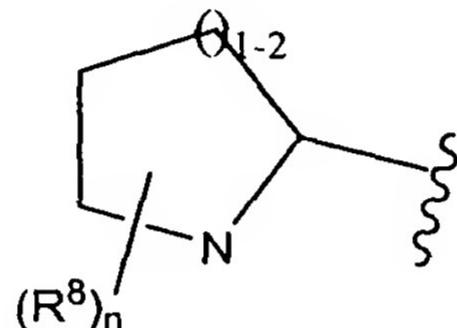
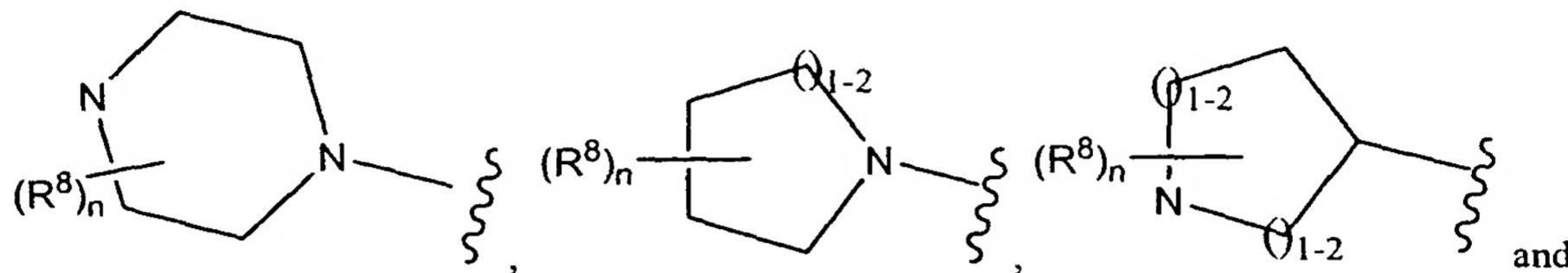
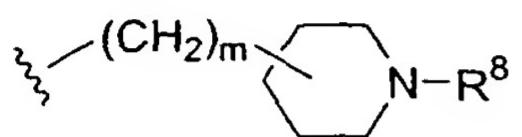


- 20 wherein each of said aryl, heteroaryl, arylalkyl and heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, cycloalkyl, CF₃, CN, -OCF₃, -OR⁶, -C(O)R⁷, -NR⁶R⁷, -C(O)OR⁶, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁶)C(O)R⁷ and

$-N(R^5)C(O)NR^5R^6;$

R^3 is selected from the group consisting of H, halogen, $-NR^5R^6$, CF_3 , alkyl, cycloalkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkynyl, alkenyl, $-(CHR^5)_n$ -aryl, $-(CHR^5)_n$ -heteroaryl, $-(CHR^5)_n$ -OR⁶, $-S(O_2)R^6$, $-C(O)R^6$,

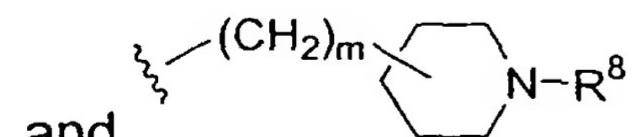
- 5 $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, $-CH(aryl)_2$, $-(CH_2)_m-NR^8$,



wherein each of said aryl, alkyl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl,

- 10 heterocyclyl and heterocyclylalkyl for R^3 and the heterocyclyl moieties whose structures are shown immediately above for R^3 can be substituted or optionally independently substituted with one or more moieties which moieties can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3 , CN, $-OCF_3$, $-OR^5$, $-C(R^4R^5)_nOR^5$, $-NR^5R^6$, $-C(R^4R^5)_nNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

- 15 R^4 is selected from the group consisting of H, halogen, CF_3 , alkyl, cycloalkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkynyl, alkenyl, $-(CHR^5)_n$ -aryl, $-(CHR^5)_n$ -heteroaryl, $-(CHR^5)_n$ -OR⁶, $-S(O_2)R^6$, $-C(O)R^6$, $-S(O_2)NR^5R^6$, $-C(O)OR^6$, $-C(O)NR^5R^6$, cycloalkyl, $-CH(aryl)_2$, $-(CH_2)_m-NR^8$,



- 20 and , wherein each of said aryl, alkyl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3 , CN, $-OCF_3$, $-OR^5$, $-NR^5R^6$, $-C(O_2)R^5$, $-C(O)NR^5R^6$, $-SR^6$,

- 25

-S(O₂)R⁶, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁵R⁶;

R⁵ is H, alkyl or aryl;

R⁶ is selected from the group consisting of H, alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, wherein

- 5 each of said alkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁵R¹⁰,
- 10 -N(R⁵)Boc, -C(R⁴R⁵)OR⁵, -C(O)R⁶, -C(O)OR⁵, -C(O)NR⁵R¹⁰, -SO₃H, -SR¹⁰,
- S(O₂)R⁷, -S(O₂)NR⁵R¹⁰, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and
- N(R⁵)C(O)NR⁵R¹⁰;

R¹⁰ is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein

- 15 each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁴R⁵, -N(R⁵)Boc,
- 20 -(CR⁴R⁵)_nOR⁵, -C(O₂)R⁵, -C(O)NR⁴R⁵, -C(O)R⁵, -SO₃H, -SR⁵, -S(O₂)R⁷,
- S(O₂)NR⁴R⁵, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ and -N(R⁵)C(O)NR⁴R⁵;

or optionally (i) R⁵ and R¹⁰ in the moiety -NR⁵R¹⁰, or (ii) R⁵ and R⁶ in the moiety -NR⁵R⁶, may be joined together to form a cycloalkyl or heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or

- 25 optionally independently being substituted with one or more R⁹ groups;

R⁷ is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each

- 30 moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF₃, OCF₃, CN, -OR⁵, -NR⁵R¹⁰, -CH₂OR⁵, -C(O₂)R⁵, -C(O)NR⁵R¹⁰, -C(O)R⁵, -SR¹⁰, -S(O₂)R¹⁰, -S(O₂)NR⁵R¹⁰, -N(R⁵)S(O₂)R¹⁰, -N(R⁵)C(O)R¹⁰ and

$-N(R^5)C(O)NR^5R^{10};$

R^8 is selected from the group consisting of R^6 , $-C(O)NR^5R^{10}$,

$-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(O)OR^6$ and $-S(O_2)R^7$;

R^9 is selected from the group consisting of halogen, CN, NR^5R^{10} ,

5 $-C(O)OR^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-C(O)R^7$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$,

$-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

R^{11} is H, alkyl or aryl;

m is 0 to 4; and

n is 1-4.

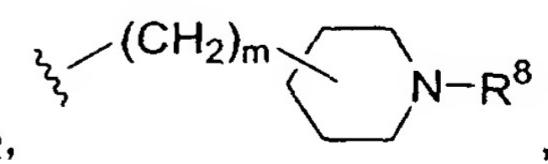
10 2. The compound of claim 1, R is selected from the group consisting of aryl, heteroaryl, alkyl, arylalkyl, heteroarylalkyl, $-S(O_2)R^7$ and $-C(O)R^7$, wherein each of said alkyl, aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl,

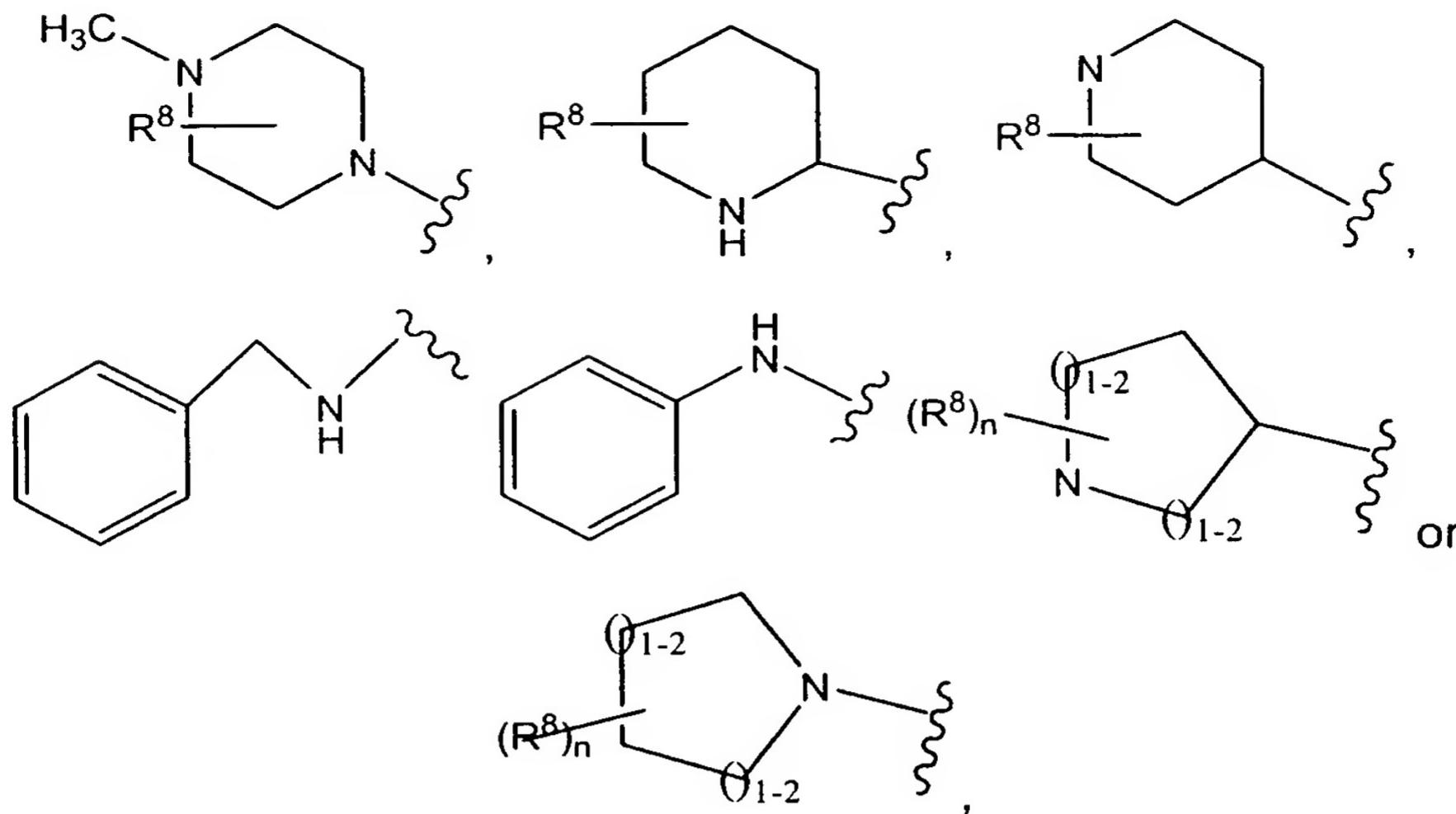
15 CF_3 , CN, $-OCF_3$, $-NR^6R^7$, $-NR^6C(O)R^8$ and $-OR^6$; and R^7 is alkyl, phenyl or pyridyl, with each of said alkyl, phenyl and pyridyl for R^7 being unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, CN, CF_3 , alkyl, $-S(O_2)R^7$, $-S(O_2)NR^6R^7$, $-N(R^5)S(O_2)R^7$, and

20 $-N(R^6)C(O)R^8$;

R^2 is selected from the group consisting of H, halogen, alkyl, alkynyl, alkenyl, aryl, heteroaryl and $-C(O)R^7$, wherein each of said alkyl, alkynyl, alkenyl, aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, CF_3 , CN, $-OCF_3$, and $-OR^6$;

R^3 is selected from the group consisting of H, aryl, heteroaryl, $-(CHR^5)_n$ -aryl, $-(CHR^5)_n$ -heteroaryl,

$-(CHR^5)_n$ -OR⁶, $-C(O)R^6$, cycloalkyl, $-NR^5R^6$, $-CH(aryl)_2$, 



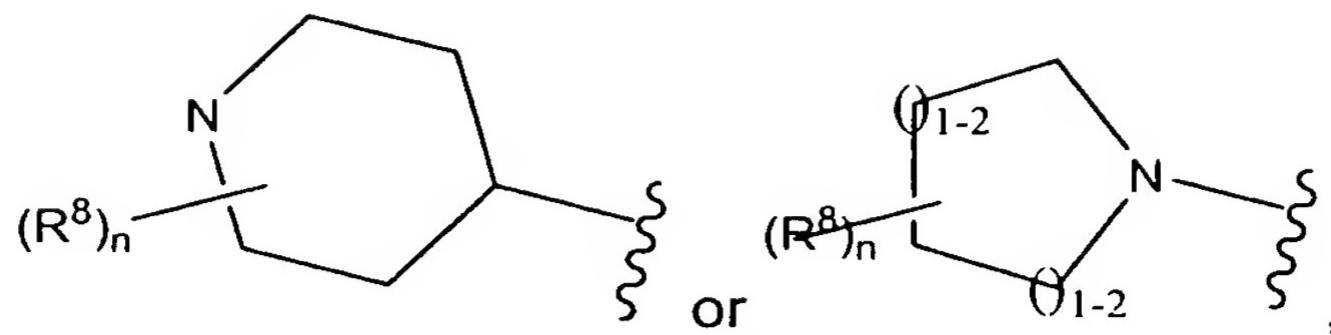
5 wherein each of said aryl, cycloalkyl and heteroaryl and the heterocyclyl
structures shown immediately above for R³ can be substituted or optionally
independently substituted with one or more moieties which can be the same or
different, each moiety being independently selected from the group consisting of
halogen, CF₃, OCF₃, alkyl, CN, aryl, -C(O)R⁵, -C(O₂)R⁵, -S(O₂)R⁶, -C(=NH)-NH₂,
10 -C(=CN)-NH₂, hydroxyalkyl, alkoxy carbonyl, -SR⁶, and OR⁵, with the proviso that
no carbon adjacent to a nitrogen atom on a heterocyclyl ring carries a -OR⁵
moiety;

15 R⁴ is selected from the group consisting of H, alkyl, aryl, heteroaryl, -
(CHR⁵)_n-aryl, - (CHR⁵)_n-heteroaryl, -(CHR⁵)_n-OR⁶, -C(O)R⁶, cycloalkyl, -CH(aryl)₂
and

15 wherein each of said aryl and heteroaryl can be substituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, CF₃, CN, -C(O₂)R⁵ and -S(O₂)R⁶;

20 R⁵ is R⁶ is H, aryl or lower alkyl;
R¹¹ is H or lower alkyl;
m is 0 to 2, and
n is 1 to 3.

3. The compound of claim 2, wherein R is selected from the group consisting of phenyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzyl, pyridylmethyl, pyrazinylmethyl, pyridazinylmethyl, pyrimidinylmethyl, -S(O₂)aryl, -S(O₂)heteroaryl, -S(O₂)alkyl, -C(O)alkyl, -C(O)aryl, and -C(O)heteroaryl, wherein
5 each of said phenyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, alkyl, aryl and heteroaryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of Cl, Br, I, lower alkyl, CF₃, CN, -C(O)OR⁶, -OCF₃, -N(H)C(O)alkyl, alkoxy and -OH.
- 10 4. The compound of claim 3, wherein R is unsubstituted phenyl, unsubstituted pyridyl, benzyl whose phenyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, CF₃, and -N(H)C(O)CH₃, pyridylmethyl whose pyridyl can be unsubstituted or optionally independently substituted with one or more moieties
15 selected from the group consisting of F, Cl, Br, CN, CF₃, and -N(H)C(O)CH₃, phenylsulfonyl whose phenyl can be unsubstituted or optionally substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, -N(H)C(O)CH₃ and CF₃, or pyridylsulfonyl whose pyridyl can be unsubstituted or optionally substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, -N(H)C(O)CH₃ and CF₃.
- 20 5. The compound of claim 4, wherein R is benzyl whose phenyl is substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, -N(H)C(O)CH₃ and CF₃.
6. The compound of claim 3, wherein R is pyridylmethyl whose pyridyl is substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, -N(H)C(O)CH₃ and CF₃.
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7. The compound of claim 3, wherein R is pyrimidinylmethyl.
8. The compound of claim 2, wherein R² is H, F, Cl, Br, hydroxyalkyl, or lower alkyl.
- 30 9. The compound of claim 8, wherein R² is H, Cl, Br, hydroxymethyl or methyl.
10. The compound of claim 2, wherein R³ is H, alkyl, aryl, -NR⁵R⁶,



wherein said alkyl and aryl and the heterocyclil moieties shown immediately above for R³ can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being

- 5 independently selected from the group consisting of F, Cl, Br, CF₃, lower alkyl, hydroxyalkyl, alkoxy, -S(O₂)R⁶, and CN.

11. The compound of claim 2, wherein R⁴ is H, alkyl or aryl, wherein said alkyl or aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being

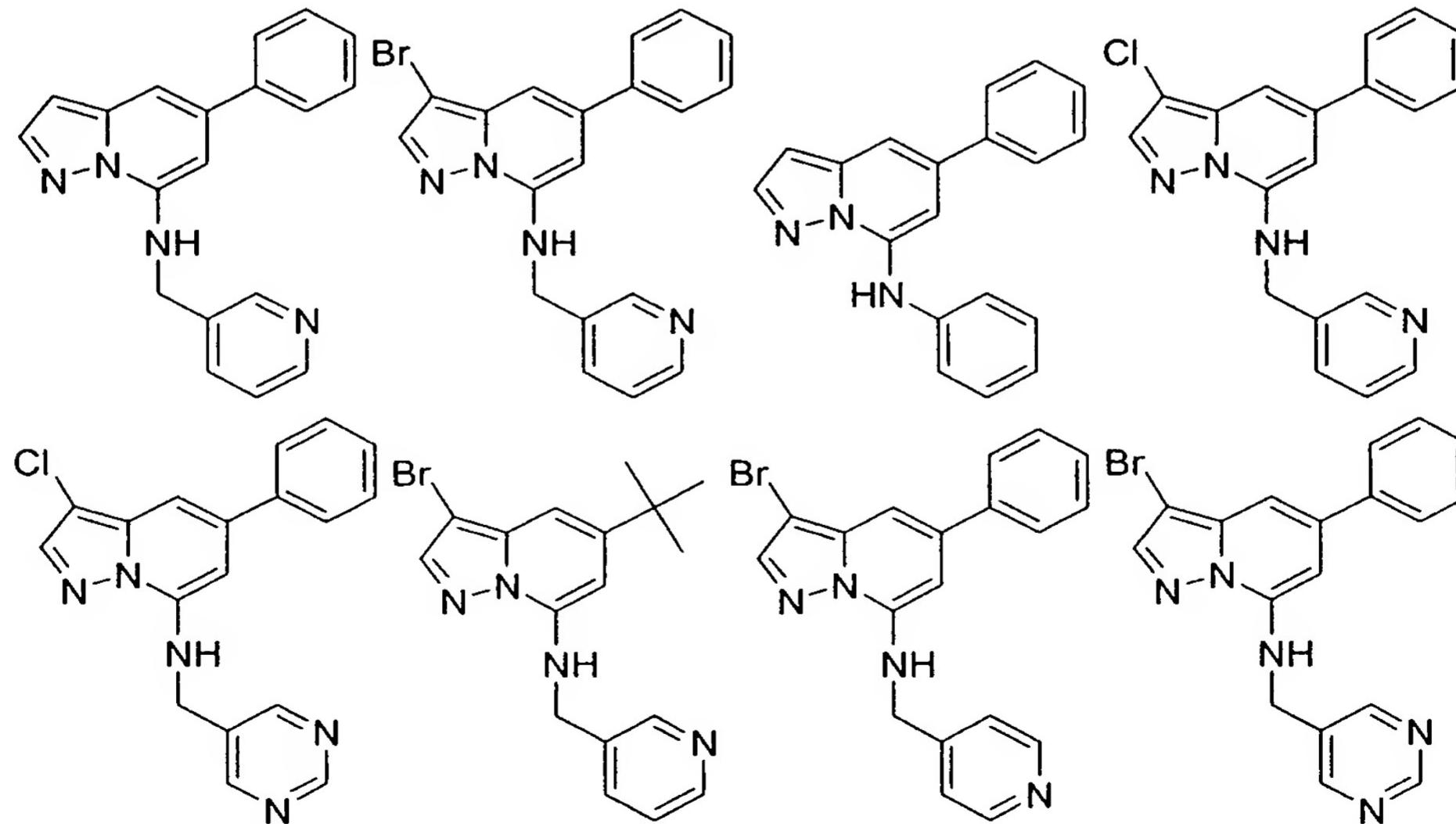
- 10 independently selected from the group consisting of F, Cl, Br, CF₃, lower alkyl, hydroxyalkyl, alkoxy, -S(O₂)R⁶, and CN.

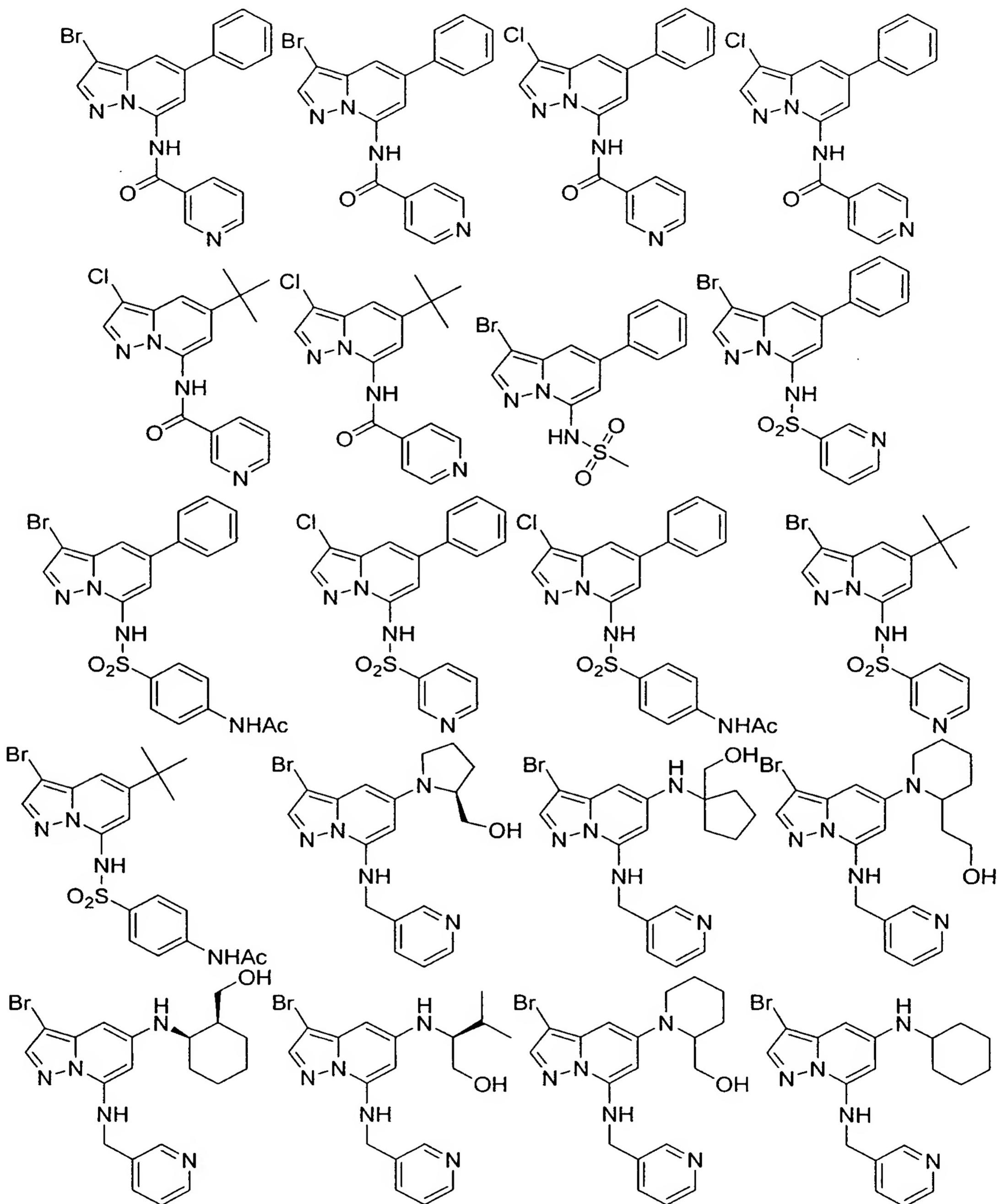
12. The compound of claim 2, wherein R⁵ is H.

13. The compound of claim 2, wherein m is 0.

14. The compound of claim 2, wherein n is 1.

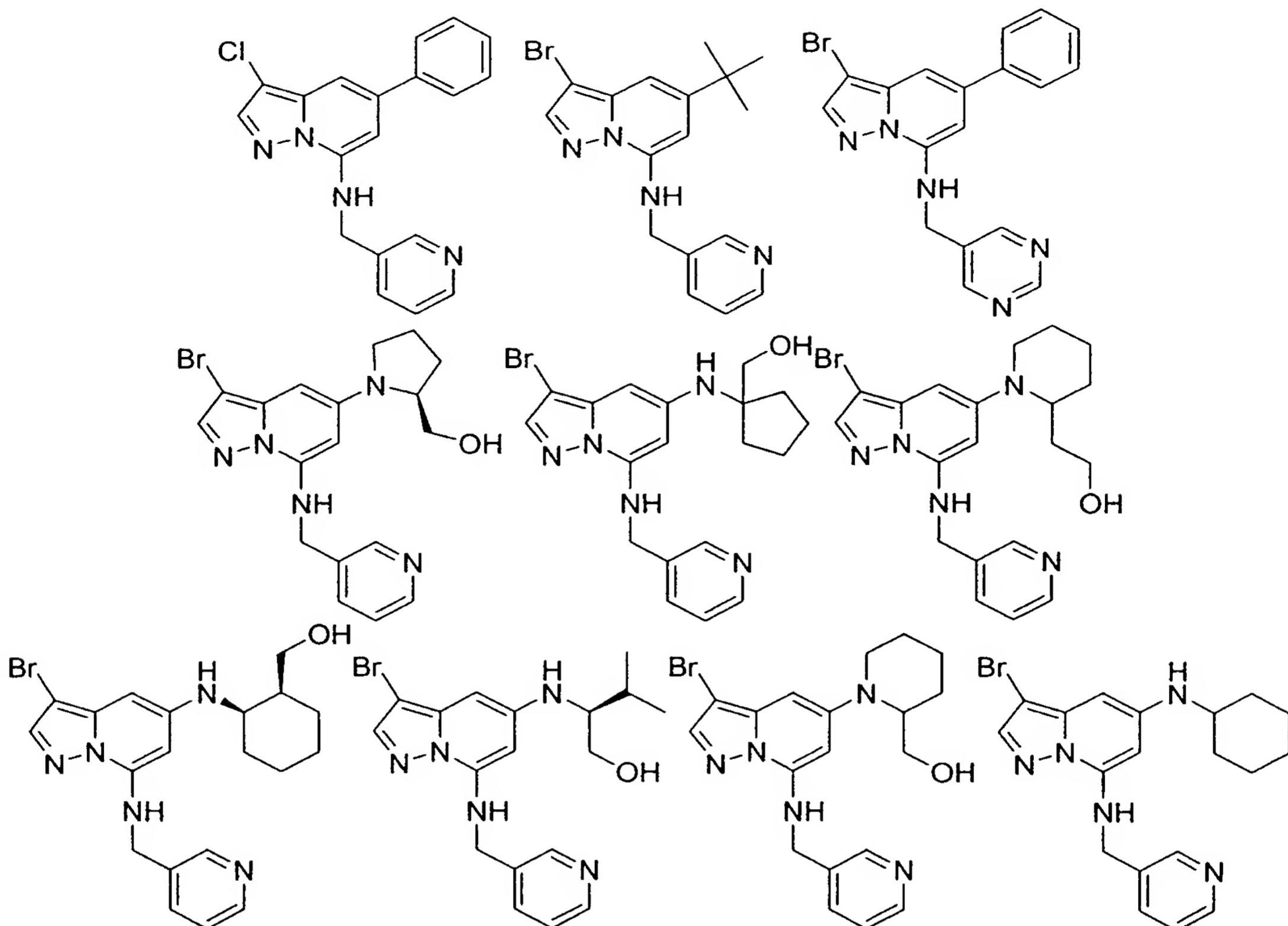
15. A compound of the formula:





or a pharmaceutically acceptable salt or solvate thereof.

16. A compound of the formula:



- 5 or a pharmaceutically acceptable salt or solvate thereof.
17. A method of inhibiting one or more cyclin dependent kinases, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such inhibition.
18. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such treatment.
19. The method of claim 18, wherein said cyclin dependent kinase is CDK2.
20. The method of claim 18, wherein said cyclin dependent kinase is mitogen activated protein kinase (MAPK/ERK).
21. The method of claim 18, wherein said cyclin dependent kinase is glycogen synthase kinase 3 (GSK3beta).
22. The method of claim 18, wherein said disease is selected from the group consisting of:

cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia;

fibrosarcoma, rhabdomyosarcoma;

astrocytoma, neuroblastoma, glioma and schwannomas; melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

23. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering to a mammal in need of such treatment

an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof;
and

an amount of at least one second compound, said second compound being an anti-cancer agent;

wherein the amounts of the first compound and said second compound result in a therapeutic effect.

24. The method of claim 22, further comprising radiation therapy.

25. The method of claim 23, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan (or CPT-11), camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, 5-Fluorouracil, temozolomide, cyclophosphamide, 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, tipifarnib, L778,123 (a farnesyl protein transferase inhibitor), BMS 214662 (a farnesyl protein transferase inhibitor), Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine,

- Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman,
Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine,
Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine,
6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin,
- 5 Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin,
Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin,
Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol,
Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate,
Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone,
- 10 Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone,
Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide,
Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine,
Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole,
Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine..
- 15 26. A pharmaceutical composition comprising a therapeutically effective
amount of at least one compound of claim 1 in combination with at least one
pharmaceutically acceptable carrier.
27. The pharmaceutical composition of claim 25, additionally comprising one or
more anti-cancer agents selected from the group consisting of cytostatic agent,
- 20 cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar,
topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil,
methotrexate, 5-fluorouracil, temozolomide, cyclophosphamide, 4-[2-[4-[(11R)-
3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-]
1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide, Zarnestra[®] (tipifarnib),
- 25 L778,123 (a farnesyl protein transferase inhibitor), BMS 214662 (a farnesyl protein
transferase inhibitor), Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C,
adriamycin, cytoxin, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide,
Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine,
Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin,
- 30 Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine,
Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine,
Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin,

- Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene,
- 5 Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.
- 10 28. A compound of claim 1, in isolated and purified form.